

RNA Binding Protein-mediated Post-transcriptional Networks Regulating HPSC Pluripotency

Grant Award Details

RNA Binding Protein-mediated Post-transcriptional Networks Regulating HPSC Pluripotency

Grant Type: Basic Biology I

Grant Number: RB1-01413

Project Objective: To comprehensively identify the transcribed RNAs in hESCs that are directly targeted by 1) LIN28 and 2) AGO2-mediated miRNA towards understanding pluripotency.

Investigator:

Name: Eugene Yeo

Institution: University of California, San Diego

Type: PI

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Cell Line Generation: iPS Cell

Award Value: \$1,308,901

Status: Closed

Progress Reports

Reporting Period: Year 1

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Reporting Period: Year 3

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Grant Application Details

Application Title: RNA Binding Protein-mediated Post-transcriptional Networks Regulating HPSC Pluripotency

Public Abstract: Human embryonic stem cells (hESC) have the remarkable capacity to replicate indefinitely and differentiate into virtually any cell type in the human body. Maintaining this pluripotent cell state requires the precise control of hundreds, if not thousands of proteins in the cells, a process known as gene regulation. Recently it has been shown that adult human cells can be induced to revert back to earlier stages of development and exhibit properties similar to hESCs. The exact method for "reprogramming" is still being optimized but currently requires inserting multiple genes into adult cells and then exposing them to the appropriate environment suitable for hESC growth, to produce these "induced pluripotent stem (iPS) cells". Generation of patient-specific iPS cells will be of tremendous benefit to disease-related biomedical research and therapy. It is of interest that many of these genes are hESC enriched or specific to pluripotent stem cells, thus understanding the regulation of genes important for pluripotency is of strong benefit to reprogramming as well.

Genes are regulated at many different levels, beginning with the production of RNAs in the nucleus (transcription), and ending with the generation of proteins from processed RNAs in the cytoplasm (translation). While much is known about the transcriptional control of gene expression involved in maintain the pluripotency of stem cells, relatively little is known about what happens to the RNAs after transcription (post-transcriptional control, or PTC), before translation. RNA binding proteins (RBPs) associate with RNAs during this intermediate stage, several of which bind directly to RNAs (targets), while others interact indirectly with RNAs via small non-coding RNAs called microRNAs to change the expression of target RNAs.

The goal of the proposed research is to produce a comprehensive map of RNAs that are targeted by RBPs important for pluripotency in stem cells, as well as uncover how these RBPs regulate their target RNAs. We will use a modification of a high throughput biochemical strategy to identify the precise location on RNAs that are in contact with carefully chosen RBPs. We will isolate and sequence millions short nucleotides representing stretches of these RNAs and map them to the human genome, together representing the complete post-transcriptional controlled regions of pluripotent stem cells. Completion of the proposed research is expected to improve our understanding of the gene regulatory mechanisms in human pluripotent stem cells, which in turn will facilitate the development of new strategies for stem cell based therapeutics and enhance reprogramming of patient-specific adult cells.

Statement of Benefit to California: Our research is aimed at providing the foundation for understanding the molecular mechanisms that maintain the pluripotent state of human ES cells and enhance reprogramming of adult cells. This in turn helps us to design novel strategies to distinguish differentiated from pluripotent stem cells for mass production of cells for therapy, manipulate stem cells to differentiate into specific cells types and enhance reprogramming of patient-specific adult cells for disease modeling and screening of compounds for new drugs. In particular, the generation of disease-specific and genetically diverse stem cell lines aided by our research will have great potential for California health care patients, pharmaceutical and biotechnology industries in terms of improved human models for drug discovery and toxicological testing. This knowledge base will directly support our efforts as well as other Californian researchers to study stem cell biology and design new therapies, and keep California's position as a strong leader in clinical research developments.

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